



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/537,204	02/06/2007	Jian-Bing Fan	067234-0130	3434

41552 7590 09/15/2010
MCDERMOTT, WILL & EMERY
11682 EL CAMINO REAL
SUITE 400
SAN DIEGO, CA 92130-2047

EXAMINER

LU, FRANK WEI MIN

ART UNIT	PAPER NUMBER
----------	--------------

1634

NOTIFICATION DATE	DELIVERY MODE
-------------------	---------------

09/15/2010

ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

SIP_Docket@mwe.com

Office Action Summary	Application No. 10/537,204	Applicant(s) FAN, JIAN-BING	
	Examiner FRANK W. LU	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 02 July 2010.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-30 is/are pending in the application.
- 4a) Of the above claim(s) 6-29 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-5 and 30 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 6/3/2005 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Response to Amendment

1. Applicant's response to the office action filed on July 2, 2010 have been entered. The claims pending in this application are claims 1-30 wherein claims 6-29 have been withdrawn due to the restriction requirement mailed on July 30, 2009. Rejection and/or objection not reiterated from the previous office action are hereby withdrawn in view of applicant's amendment filed on July 2, 2010. Therefore, claims 1-5 and 30 will be examined.

Information Disclosure Statement

2. The examiner notes that applicant has not provided documents 215, 228, 255, 259, 264, 266, 269, and 270 in the information disclosure statement filed on December 26, 2007. The documents 229 and 263 in the information disclosure statement filed on December 26, 2007 are books. However, applicant has not provided whole books for documents 229 and 263. Therefore, documents 215, 228, 229, 255, 259, 263, 264, 266, 269, and 270 have been struck through in the form-1449 filed on December 26, 2007. Note that applicant has not addressed this issue.

Election/Restrictions

3. This application contains claims 6-29 drawn to an invention nonelected in the reply filed on November 30, 2009. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

Art Unit: 1634

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Enablement

Claims 1-5 and 30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

“Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.”

The nature of the invention

The claims are drawn to a method for multiplex detection of methylated target sequences on target nucleic acids. The invention is a class of invention which the CAFC has characterized as “the unpredictable arts such as chemistry and biology” *Mycogen Plant Sci., Inc. v. Monsanto Co.*, 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The Breadth of The Claims

Art Unit: 1634

Claims 1-5 and 30 are directed to a method for multiplex detection of methylated target sequences on target nucleic acids by detecting the presence of said first population comprising non-cleaved target nucleic acids wherein the presence of said first population comprising non-cleaved target nucleic acids indicates the presence of methylated target nucleic acids in said first population when said first population of target nucleic acids are any kind of nucleic acid and said non-cleaved target nucleic acids are generated by any kind of enzyme.

Working Examples

The specification provides no working example related to the claimed inventions recited in claims 1-5 and 30 wherein the presence of said first population comprising non-cleaved target nucleic acids indicates the presence of methylated target nucleic acids in said first population when said first population of target nucleic acids are any kind of nucleic acid and said non-cleaved target nucleic acids are generated by any kind of enzyme.

The Amount of Direction or Guidance Provided and The State of The Prior Art

The specification does not provide a guidance to show that the presence of said first population comprising non-cleaved target nucleic acids indicates the presence of methylated target nucleic acids in said first population when said first population of target nucleic acids are any kind of nucleic acid and said non-cleaved target nucleic acids are generated by any kind of enzyme. Furthermore, there is no experimental data in the specification to support the claimed invention recited in claims 1-5 and 30. Although it is known in the prior art that some restriction enzyme such as Hpa II can not digest specific methylated nucleotides in a DNA sequence (see

Art Unit: 1634

attached document for HpaII from NEB), during the process of the prior art search, the examiner has not found any prior art which is related to the methods as recited in claims 1-5 and 30 .

Level of Skill in The Art, The Unpredictability of The Art, and The Quantity of Experimentation Necessary

While the relative skill in the art is very high (the Ph.D. degree with laboratory experience), there is no predictability whether the methods recited in claims 1-5 and 30 can be performed by detecting the presence of said first population comprising non-cleaved target nucleic acids wherein the presence of said first population comprising non-cleaved target nucleic acids indicates the presence of methylated target nucleic acids in said first population when said first population of target nucleic acids are any kind of nucleic acid and said non-cleaved target nucleic acids are generated by any kind of enzyme. Furthermore, there is no experimental data in the specification to support the claimed invention recited in claims 1-5 and 30.

First, since step (d) of claim 1 does not require that said first population of target nucleic acids is specific nucleic acids and non-cleaved nucleic acids are generated after digesting said first population of target nucleic acids with an enzyme that selectively cleaves at said target sequences that are unmethylated and it is known that exonuclease I is a 3' to 5' single strand exonuclease (see attached document for exonuclease I from NEB), when said first population of target nucleic acids comprises a double stranded DNA having a single strand on its 3' end and cleaved nucleic acids are generated after digesting said first population of target nucleic acids with any kind of enzyme such as exonuclease I, it is unclear how the presence of said first

Art Unit: 1634

population comprising non-cleaved target nucleic acids generated by exonuclease I can indicate the presence of methylated target nucleic acids in said first population.

Second, since claim 4 does not require that a plurality of target probes only hybridizes with non-cleaved target nucleic acids and claim 5 is dependent on claim 4, if some of target probes hybridize with cleaved target nucleic acids, it is unclear how to differentiate said non-cleaved target nucleic acids and said non-cleaved target nucleic acids, how detecting the presence of said probes can be used as an indication of the presence of methylated target nucleic acid as recited in claim 4 and how detecting said amplicons can be used as an indication of the presence of methylated target nucleic acid as recited in claim 5.

Third, since Msp I can cut both CpG methylated and unmethylated DNA sequences (see attached document for Msp I from NEB) while claim 1 requires that said enzyme selectively cleaves at said target sequences that are unmethylated, it is unclear how Msp I can selectively cleaves at said target sequences that are unmethylated as recited in claim 1 and the digestion by Msp I can be blocked by methylation at a cytosine as recited in claim 5.

Therefore, in view of above discussions, it is concluded that undue experimentation is required to make the invention as it is claimed. The undue experimentation at least includes to test whether the methods recited in claims 1-5 and 30 can be performed by detecting the presence of said first population comprising non-cleaved target nucleic acids wherein the presence of said first population comprising non-cleaved target nucleic acids indicates the presence of methylated target nucleic acids in said first population when said first population of target nucleic acids are any kind of nucleic acid and said non-cleaved target nucleic acids are target nucleic acids are generated by any kind of enzyme.

Art Unit: 1634

Conclusion

In the instant case, as discussed above, the level of unpredictability in the art is high, the specification provides one with no guidance that leads one to claimed methods. One of skill in the art cannot readily anticipate the effect of a change within the subject matter to which the claimed invention pertains. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of any working examples related to the claimed inventions and the no teaching in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the methods of the claims as broadly written.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-5 and 30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Claim 1 is rejected as vague and indefinite in view of step (c) because it is unclear that said target nucleic acids are from a first population or a second population or both said first population and said second population. If said target nucleic acids are only from a first population, it is unclear why step (b) is required in the method. Please clarify.

9. Claim 1 recites the limitation “said first population comprising non-cleaved target nucleic acid” in step (d) of the claim. There is insufficient antecedent basis for this limitation in the

Art Unit: 1634

claim because step (a) only has a phrase “a first population of target nucleic acids” and does not contain “a first population comprising non-cleaved target nucleic acid”. Please clarify.

10. Claim 4 is rejected as vague and indefinite in view of step (e) (i) because it is unclear that a target nucleic acid is from said immobilized target nucleic acids or not. Please clarify.

11. Claim 4 is rejected as vague and indefinite in view of step (e) (ii) because it is unclear where a methylated target sequence comes from. Please clarify.

12. Claim 4 is rejected as vague and indefinite in view of step (f) because it is unclear that said probe is from the hybridization complexes or not. Please clarify.

13. Claim 5 is rejected as vague and indefinite in view of (i) because it is unclear that said probe is from the hybridization complexes or not. Please clarify.

14. Claim 30 is rejected as vague and indefinite. Since MspI can cut both CpG methylated and unmethylated DNA sequences (see attached document for Msp I from NEB) while claim 1 requires that said enzyme selectively cleaves at said target sequences that are unmethylated, claims 1 and 30 do not correspond each other. Please clarify.

15. Claim 30 recites the limitation “the digestion” in the claim. There is insufficient antecedent basis for this limitation in the claim since there is no word “digestion” in claim 1. Please clarify.

16. Claim 30 is rejected as vague and indefinite because it is unclear where a cytosine is located on. Please clarify.

Conclusion

17. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

18. No claim is allowed.

19. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is (571)273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

Art Unit: 1634

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen, can be reached on (571)272-0731.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Frank W Lu /
Primary Examiner, Art Unit 1634
September 9, 2010